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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/308,223	08/12/1999	GEORG KALLMEYER	P8341-9011	5876

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/308,223	**Applicant(s)** KALLMEYER ET AL.	
	Examiner Brandon J. Fetterolf, PhD	**Art Unit** 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 31 January 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *13,15-18 and 22-36*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
3/30/06

Response to the Amendment

The Amendment filed on 01/31/2006 in response to the previous Final Office Action (11/01/2006) is acknowledged and has been entered.

Claims 13, 15-18 and 22-36 are currently pending and under consideration

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13, 15-36 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Andya *et al.* (US Patent No. 6,267,958, March 1996) in view of Michaelis *et al.* (US Patent No. 5,919,443, June 1995).

Andya *et al.* teach a variety of lyophilizates comprising monoclonal or polyclonal antibodies, sugars, amino acids, and surfactants wherein the lyophilizate is essentially free of polyethylene glycols and additional proteins; wherein the lyophilizate contains a single amino acid or two different amino acids; wherein the lyophilizate further comprises a buffering agent or an isotonizing agent which is present in an amount such that a reconstituted solution of the lyophilizate has a pH value of 5-8 (columns 3-5); wherein the lyophilizate is storage-stable for a time period of at least three months at a temperature of about 4-12^{0}C (column 8, lines 45+, columns 3-5); wherein the sugar comprises at least one member selected from the group consisting of a monosaccharide, a disaccharide and a trisaccharide (column 15 line 12); wherein the sugar comprises sucrose or trehalose; wherein the amino acid comprises histidine, glutamic acid; wherein the surfactant comprises a polysorbate (column 15); wherein the monoclonal or the polyclonal antibody is directed against an antigen selected from the group consisting of integrins and or other antigens (column 7). Andya *et al.* further teach a variety of lyophilizates comprising monoclonal or polyclonal antibodies, sugars, amino acids, and surfactants, and an inorganic acid as a buffering agent (column 9, line 44); wherein the lyophilzate is dissolved in a physiologically acceptable solution; has a pH of 5-8; contains 1-10mg/ml of antibody (column 17). Andya *et al.* broadly anticipate a method of preparing a lyophilizate comprising mixing a buffered solution containing a monoclonal antibody or polyclonal antibody, a sugar, at least one amino acid and a surfactant, to prepare a mixed solution, wherein the mixed solution has a pH value of 5-8; and lyophilizing the mixed solution, wherein the lyophilizate is essentially free of polyethylene glycols and additional proteins. Further the molar concentrations of sugars, amino acids, and surfactants as claimed in claims 31-33 are also anticipated by Andya *et al.* (see columns 3-5).

Andya *et al.* do not include the teachings of an amino sugar such as glucosamine, N-methyl-glucosamine, galactosamine, and neuraminic acid.

Michaelis *et al.* teach the advantages of an improved lyophilizate which contains amino sugars (column 4,lines 1-6)

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to modify the lyophilizate of Andya *et al.* so as to include an amino sugar as taught by Michaelis *et al.* One would have been motivated to do so because Michaelis *et al.* make the surprising discovery that it is possible to produce stable forms of pharmaceutical agents when

maltose, raffinose, sucrose, trehalose or amino sugars are used as additives (column 3, line 9). Michaelis *et al.* further teach that solid preparations which contain maltose, raffinose, sucrose, trehalose or amino sugars as auxiliary agents can be frozen or even stored at increased temperatures with no significant loss of protein quality. Hence, the teachings of Michaelis *et al.* suggest an improved and more versatile lyophilizate which can also contain amino sugar.

In response to this rejection, Applicants respectfully point out that amoung proteins different stabilizers are required, not all stabilizers are suitable for all proteins. For example, Applicants submit that Osterberg (WO 94,07510, IDS) state on page 4, lines 25-32 that:

> "Proteins are different with regard to physio-chemical properties. When preparing a pharmaceutical preparation which should be physico-chemical acceptable, and stable for a long time, consideration cannot only be taken to the physiological properties of the protein but also other aspects must be considered such as industrial manufacture, easy handling for the patient and safety for the patient. **The results of these aspects are not predictable when testing different formulations and there often is a unique solution for each protein**," (emphasis added).

As such, Applicants submit that Osterberg points out that different proteins are different in their physiochemical properties and thus for each protein or class of proteins an individual solution has to be developed and thus, it cannot be predicted that the same formulation will be useful for a different class of proteins. Moreover, Applicants submit that Manning (Pharmaceutical Research, Vol. 6., No. 11, 1989, p. 903-918) states on page 913, left column, first sentence of the last paragraph, that "protein stability encompasses many complicated and interrelated chemical and physical process". From this, Applicants contend that for every protein or class of proteins an individual solution has to be found due to different physical and chemical constraints. Furthermore, Applicants submit that Osterberg's and Manning's conclusions are supported by the fact that different substances are indicated as good stabilizers in some references and as not useful stabilizers in other references. For example, Applicants submit that Kunihiro (EP 0 689 843) page 4, line 4 - 7, indicates that the combination of soluble thrombomodulin together with albumin, purified gelatin, glycine, glucose or mannitol **failed** to exhibit sufficient long term stability. Thus Applicants argue that this document contradicts the contention in the office action that Michaelis' teaching can be applied to any and all pharmaceutical preparations because Kunihiro teaches away from the current invention in that the combination of an amino acid with a sugar had no beneficial effect on stability.

Applicants further point to Hanson (chapter 7 in Stability of Protein Pharmaceuticals, 1992) whom indicates on page 217, second paragraph, line 6 to 7 that "Ornithine, aspartic acid, glutamic acid, alanine and glycine did not stabilize" intravenous immunoglobulin preparations. Thus, Applicants contend that Hanson also contradicts the contention in the office action that Michaelis' teaching can be applied to any and all pharmaceutical preparations and teaches away from the current invention which shows that the use of the amino acids listed in Hanson improve the stability of the lyophilized antibody formulation. In addition, Applicants argue that Metzner (EP 0 733 702) which is equivalent to US Patent No. 6,204,036 indicates that histidine and glutamic acid alone, even without further additives, show sufficient stabilization (page 3, line 9, of the German text, column 5, lines 56-58 of the US text). In contrast to Metzner, Applicants submit that Michaelis (WO 94/14465) states on page 10, lines 4 to 7 of the German WO 94/14465 that the addition of glutamic acid has no significant impact on the storage stability. Moreover, Applicants submit that both Metzner and Michaelis indicate that the surfactant had no impact on storage stability (Metzner page 3, lines 42-43 or col. 6, lines 48-50 in the U.S. Patent, Michaelis page 9, last paragraph of WO 94/14465) but the present inventors have found that the surfactant does affect stability in the present invention. Thus, Applicants argue that formulations for stabilizing different pharmaceutical preparations clearly cannot be generalized. Moreover, Applicants assert that Nema (J. Parent Sci. Technol., 47, p. 76-83, 1993) states on page 81, left column, last sentence of the first paragraph: "A surprising result was obtained with trehalose, a disaccharide which is considered by many workers to be one of the best cryoprotectants, but proved to be ineffective in this study at a concentration of 5% W/V". In view of this, Applicants contend that this statement also supports the conclusion of the non-transferability of formulations to different classes of protein. Applicants further point out that three things can be concluded from the above references:

1) Though there are diverse citations showing that the use of a single compound can improve the stability of formulations markedly, there is no suggestion that a combination of different compounds discussed in different references will result in a formulation with further improved stability. Furthermore, there is no hint in these documents as to the particular combination of compounds as described in the current invention.

2) As can be seen from these references, it is not possible to transfer the composition of a formulation useful with one class of proteins or with one protein to other proteins. It is not probable or even predictable that such a transfer might be successful.

3) There are no cited documents that suggest or disclose that a formulation for stabilizing a non-antibody protein can be used for the stabilization of a lyophilized antibody preparation.

Applicants also point out that Michaelis shows amino sugar containing preparations in Example 5. From table 6 and 7, Applicants submit that it can be seen that a combination containing G-CSF plus a surfactant plus an amino sugar plus one amino acid has poor stability compared to formulations containing an amino sugar, a second non- amino sugar and optionally an amino acid. Thus, Applicants argue that Michaelis does not suggest the combination as claimed by the current application which uses an amino sugar, at least one amino acid and a surfactant to stabilize antibodies. Thus, Applicants contend that even if one skilled in the art were to combine Michaelis with Andya (which as discussed above, they would not) they would not arrive at the present invention. Applicants contend that one skilled in the art would not expect Michaelis' formulation to be useful for any and all pharmaceutical preparations as different proteins require different stabilization agents and there is no reason to believe that Michaelis' formulation would stabilize antibody preparations. In addition, Applicants point out that Michaelis found that a preparation similar to the present invention (which uses an amino sugar, at least one amino acid and a surfactant) resulted in less stability for G-CSF.

These arguments have been carefully considered, but are not found persuasive.

Regarding the references cited by Applicants to argue that there is no suggestion that a combination of different compounds discussed in different references will result in a formulation with further improved stability, the Examiner acknowledges and agrees with Applicants contention that there is no suggestion that **a combination of different compounds discussed in different references** will result in a formulation with further improved stability (emphasis added). However, the Examiner recognizes that the fact patterns involved in the instant situation are different from those discussed and argued by Applicants. In the instant case, Andya, a single reference, teach a lyophilizate comprising monoclonal or polyclonal antibodies, sugars, amino acids, and surfactants wherein the lyophilizate is essentially free of polyethylene glycols and additional proteins, where as Michaelis et al., a single reference, teach the advantages of an improved lyophilizate which contains

amino sugars. Thus, in agreement with Applicants statement that there are diverse citations showing that the use of a single compound can improve the stability of formulations markedly, Michaelis et al. suggests, *supra*, the motivation to combine a singe compound such as an amino sugar in the formulation taught by Andya. Moreover, it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which make up the state of the art with regard to the claimed invention. Furthermore, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, both references represent analogous teachings comprising the preparation of stable pharmaceutical compositions. In response to Applicants contention that the combination of Michaelis (Example 5, Table 6 and 7) containing G-CSF plus a surfactant plus an amino sugar plus one amino acid has poor stability compared to formulations containing an amino sugar, a second non- amino sugar and optionally an amino acid, the Examiner acknowledges applicants interpretation of the results shown in Table 6 and 7 of Example 5. However, the Examiner recognizes that Michaelis appears to teach the opposite. For example, the % DCP (decomposition product) for Formulation 11, which contains an amino sugar (N-methyl glucosamine), an amino acid (phenylalanine) and a surfactant (maltrose) was 1.2 and 1.8 at 8°C and 40°C respectively, where as the %DCP for Formulation 14 containing an amino sugar (N-methyl-glucosamine), glycine (amino acid) and a non-amino acid (Plunaria) was 1.2 and 3.5 at 8°C and 40°C respectively. As such, it appears the Formulation 11 is more stable than the Formulation of 14. Therefore, Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination.

Therefore, NO claim is allowed

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF